



U.S. Department of
Health and Human
Services



National Institutes
of Health



National Heart, Lung,
and Blood Institute

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National Heart, Lung, and Blood Institute

Randomized Clinical Trials: Research That Makes a Difference.

Third Annual NIH/OBSSR Summer Institute
on Randomized Clinical Trials

Airlie Conference Center, Warrenton, Virginia

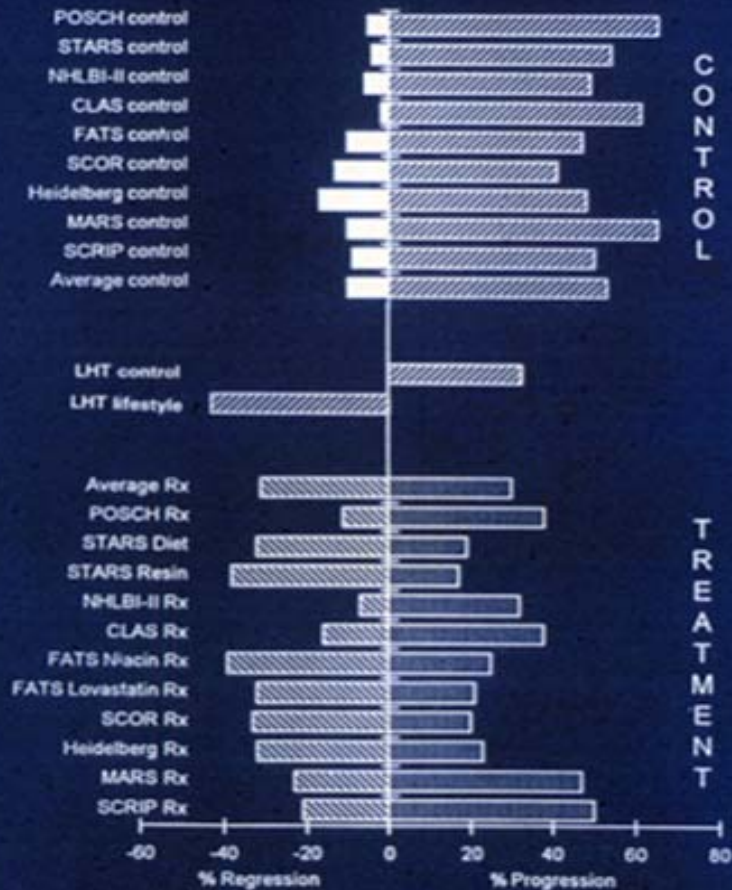
July 20, 2003

Disclosure

I have no conflicts of interest to disclose.

This talk does not necessarily reflect the views of the NHLBI.

Regression of Coronary Artery Disease by Lipid Lowering: Angiographic Evidence



Adapted from Deedwania PC. *Contemp. Issues Cardiol.* 1995;79:973

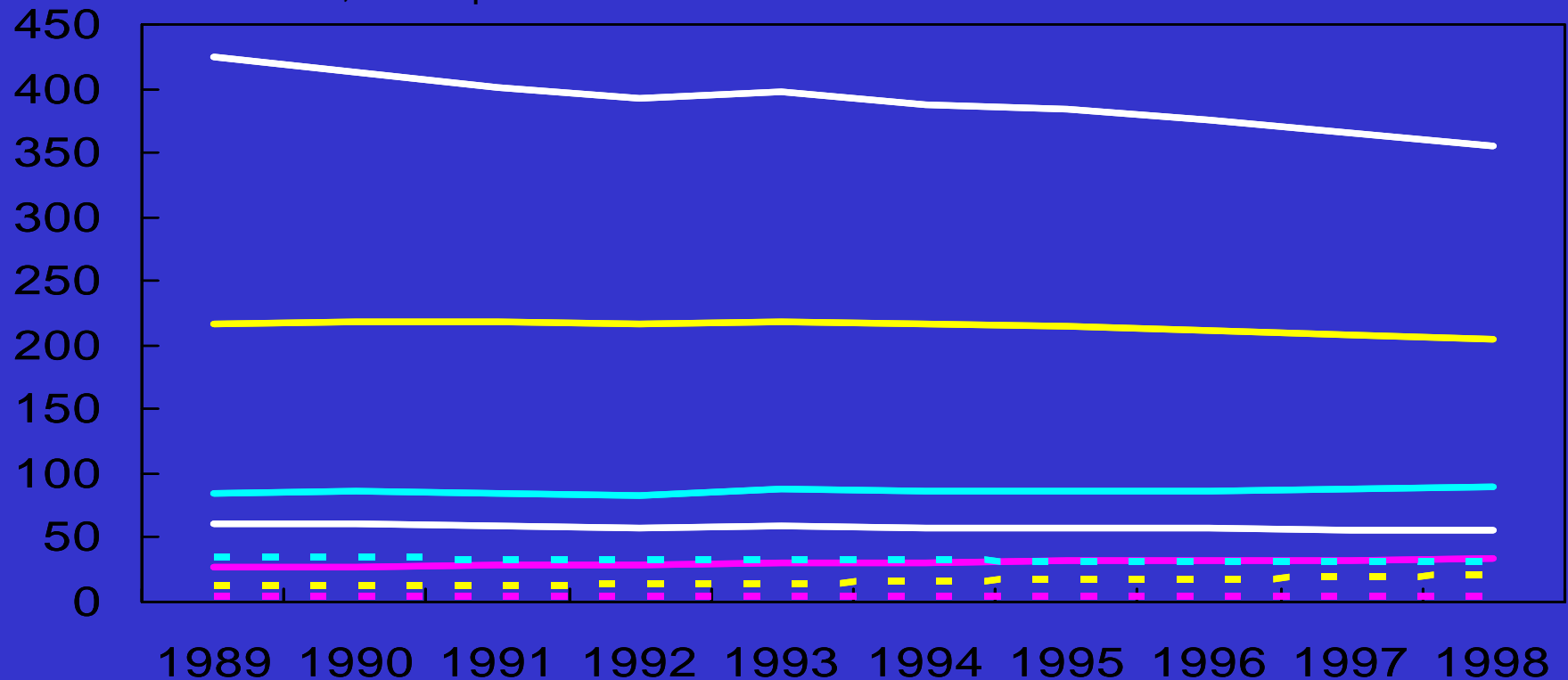
Primary Public Health Strategy

- Identification of causal, or “risk factors” for disease (biological, behavioral).
- Prevention: Reduction of exposure (primary and secondary prevention).
- Treatment: Intervening on biological mechanisms (medications, gene therapy, devices); reconstruction (surgery).
- Research: Generation of knowledge in basic and clinical sciences.



Age Adjusted Death Rates by Major Diagnosis, U.S., 1989-1998

Death/100,000 Population

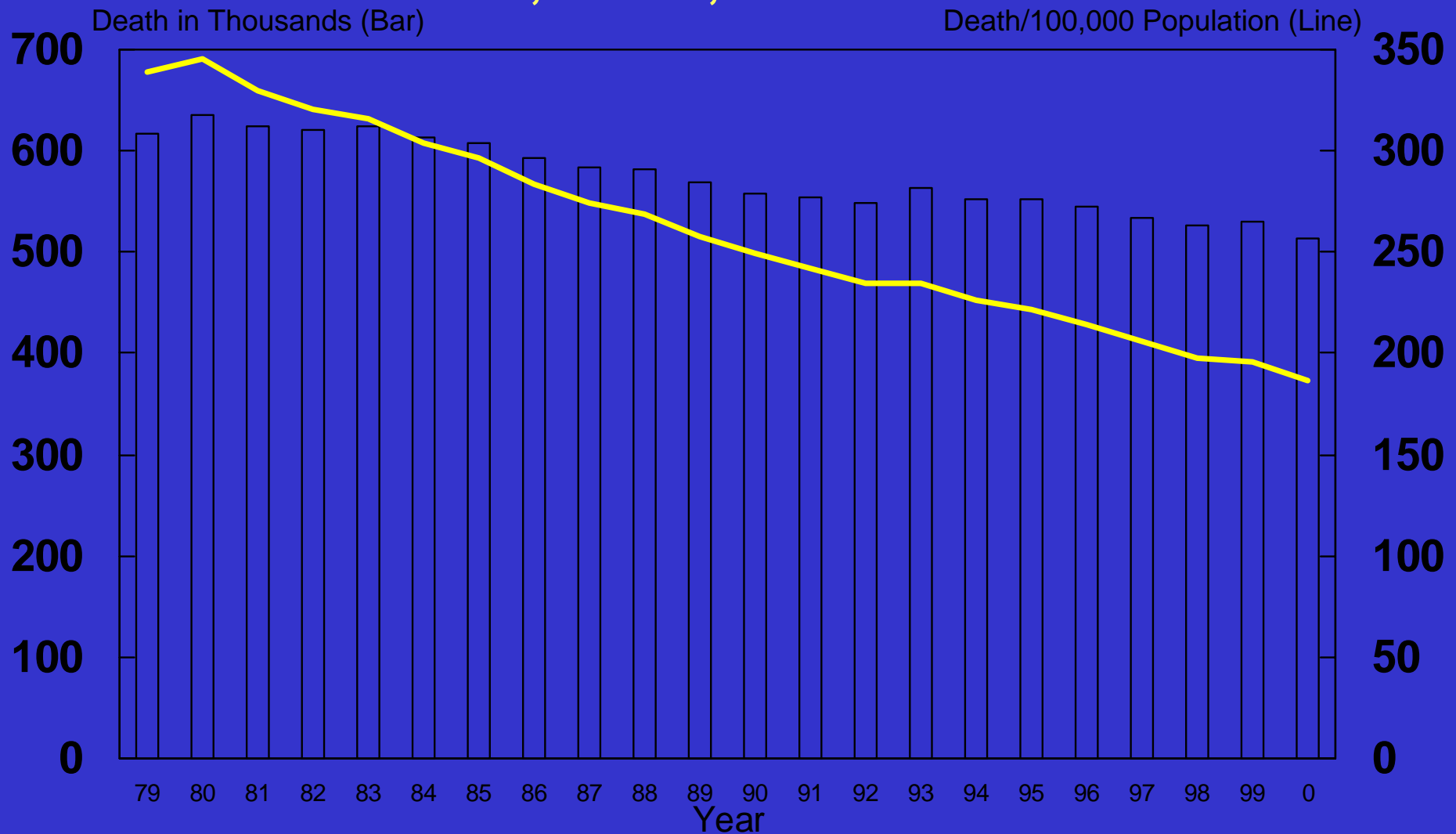


Year

- | | | |
|------------------------|---------------------|---------------|
| — Cardiovascular | — Neoplasms | — Respiratory |
| — Injury and Poisoning | — Endocrine | - - Digestive |
| - - Mental | - - Musculoskeletal | |

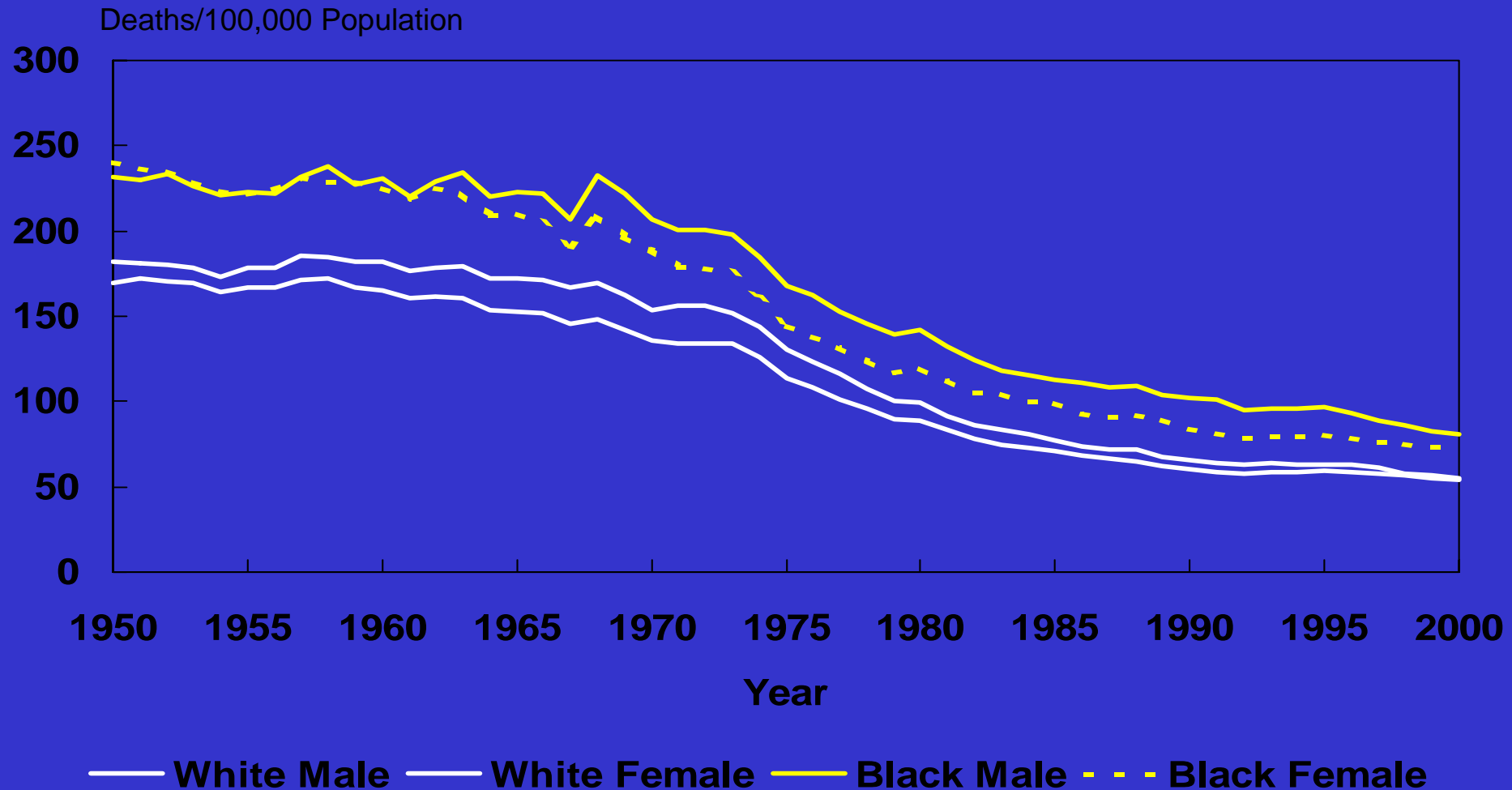


Deaths and Age-Adjusted Death Rates for CHD, U.S., 1979-2000



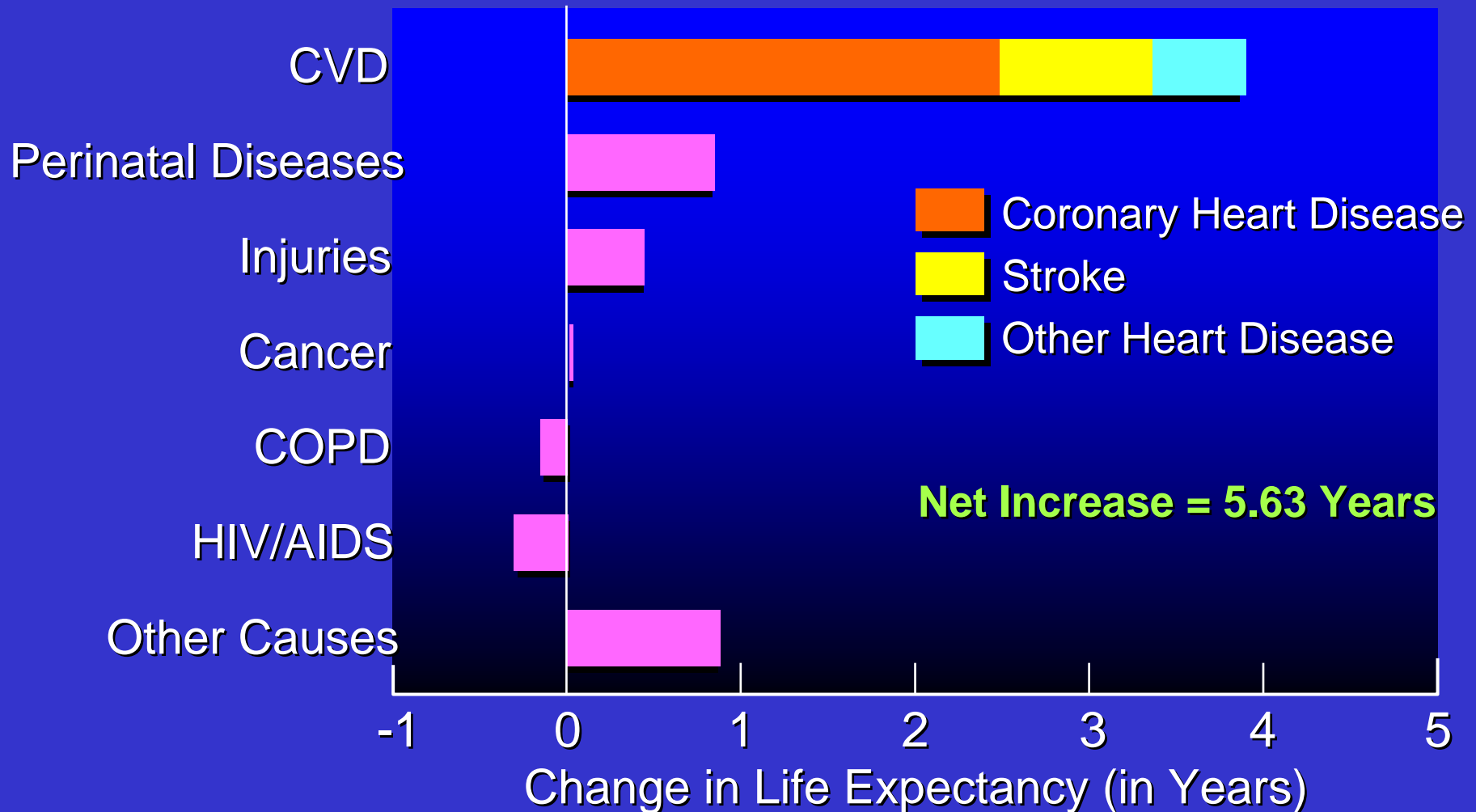


Age-Adjusted Death Rates for Stroke by Race and Sex, U.S., 1950-2000

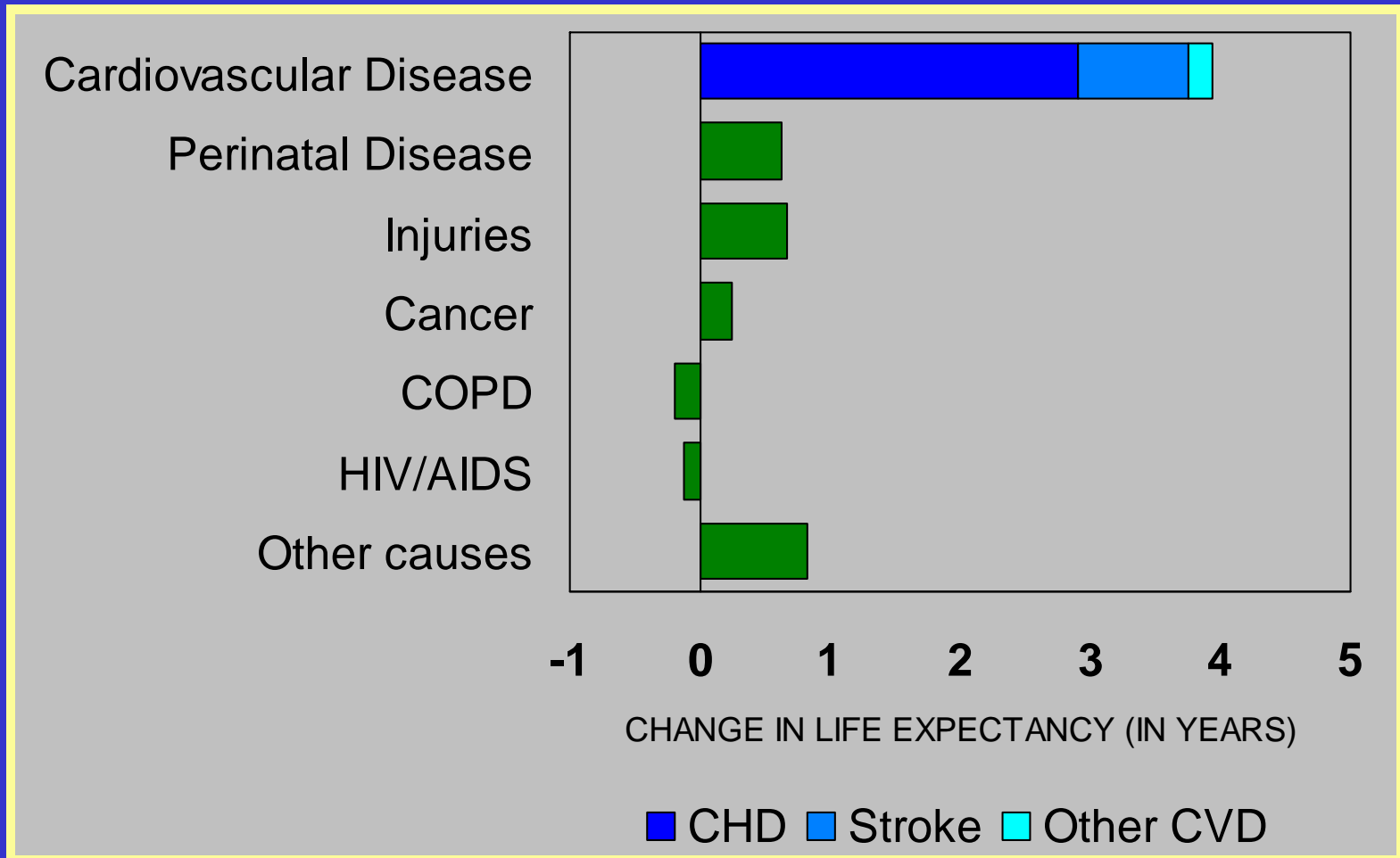


*Nonwhite from 1950-1967.

Contributions to Change in Life Expectancy, 1965-1995



CONTRIBUTIONS TO CHANGE IN LIFE EXPECTANCY, U.S., 1970 - 2000



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What contributes to decisions about care of patients?

- Diagnosis
- Prognostic markers
- Clinical research data, esp. from RCTs.
- Clinical experience
- Patient's preferences

Evidence-Based Medicine

“the conscientious, explicit, and
judicious use of current best
evidence in making decisions
about the care of individual
patients...”

David L. Sackett

BMJ, 1996

Can the strategy of risk factor identification, prevention, and treatment be effective in the case of psychosocial risk factors for somatic disorders?

Behavioral and Psychosocial CVD Risk Factors

- Behavioral/Lifestyle
 - Smoking
 - Sedentary lifestyle
 - Obesity
 - High-fat diet
- Psychosocial
 - Type A Behavior/Hostility
 - Depression
 - Low levels of social support
 - Stress

“Clinical Trial”

“A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention.”

Friedman, Furberg and DeMets, 1998

Characteristics of RCTs

- A clinically important and scientifically justified a-priori hypothesis.
- A well-defined population, and representative sample of sufficient size to detect clinically important differences between treatments.
- One or more comparison groups whose care is specified sufficiently well to allow replication.

Characteristics of RCTs

- Random assignment to treatment and control group(s).

“Randomization properly carried out...relieves the experimenter from the anxiety of considering and estimating the magnitude of the innumerable causes by which ... data may be disturbed.”

R.A. Fisher, 1935

Characteristics of RCTs

- A few well-justified outcome measures, defined a-priori and obtained either blind to treatment group or with safeguards to avoid confusing the opinions or expectations of patients or researchers with treatment effects.

Characteristics of RCTs

- A primary analysis which includes data from all randomized subjects (intent-to-treat) and pre-specified subgroups.
- A valid test for statistical significance and estimates of effect sizes to guide clinical and policy decisions.

ENRICHD

Enhancing Recovery
in Coronary Heart
Disease Patients

Study Organization

- Study Chair and Co-Chair
 - L Berkman, Harvard University, Boston, MA
 - A Jaffe, Mayo Clinic, Rochester, MN
- Coordinating Center
 - J Hosking & D Catellier, U. North Carolina at Chapel Hill
- Project Office
 - S Czajkowski, NHLBI, Bethesda, MD
- Data and Safety Monitoring Board

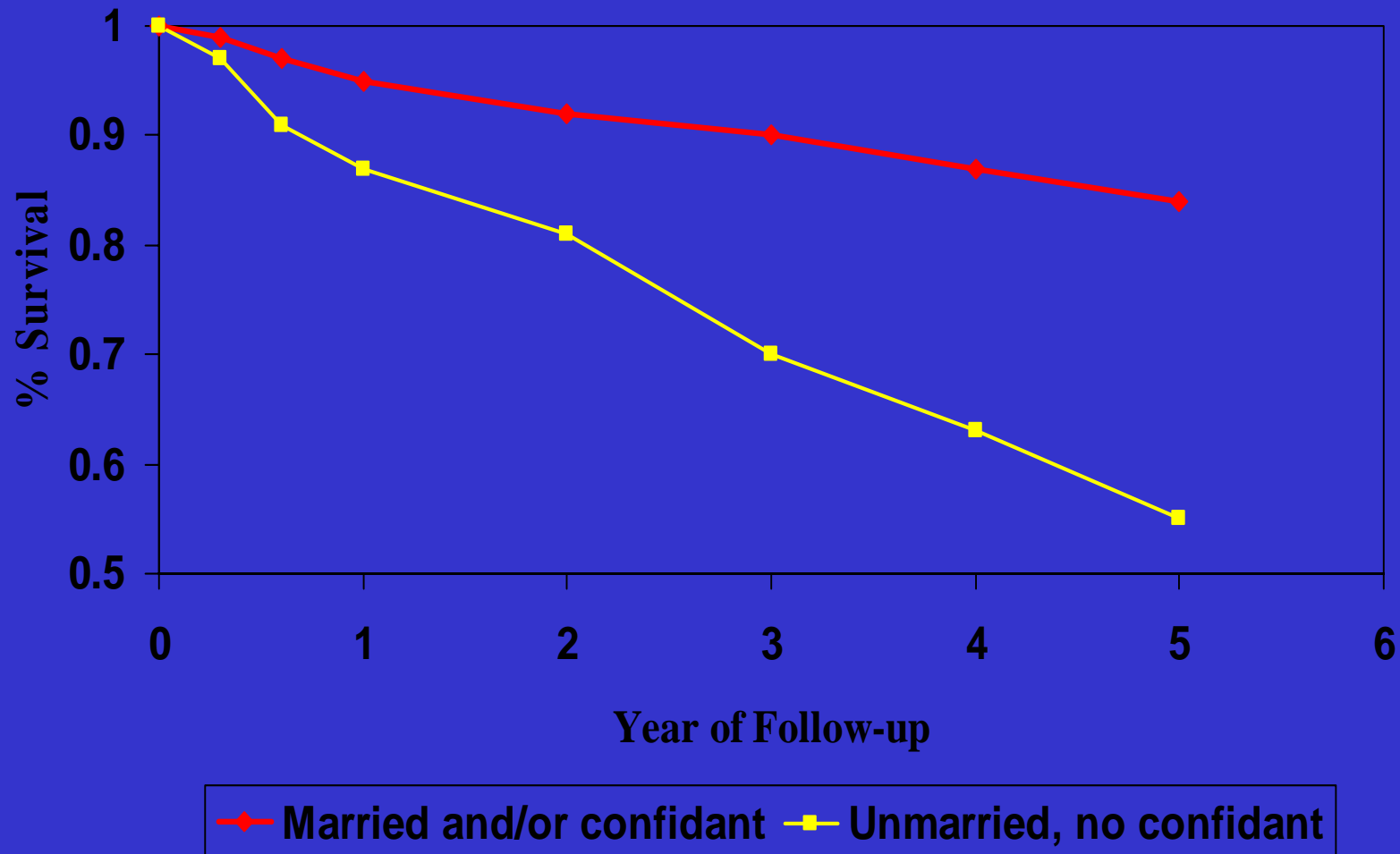
Study Organization

- Clinical sites
 - J Blumenthal, Duke University, Durham, NC
 - M Burg, Yale University, New Haven, CT
 - R Carney, Washington University, St. Louis, MO
 - R DeBusk, Stanford University, Palo Alto, CA
 - P Mitchell, Univ. of Washington, Seattle, WA
 - L Powell, Rush-Presbyterian-St. Lukes Med. Center, Chicago, IL
 - J Raczynski, Univ. of Alabama at Birmingham, AL
 - N Schneiderman, Univ. of Miami, Coral Gables, FL

Background

- Low social support also is associated with an increased risk of death and recurrent infarction
- Adjusted risks range from 2.0 – 4.0
 - Williams *JAMA*, 1992; Case, *JAMA*, 1992; Berkman, *Ann Int Med.* 1992; Gorkin, *AJC*, 1993; Kawachi, *J Epid & Comm. Hlth*, 1996.

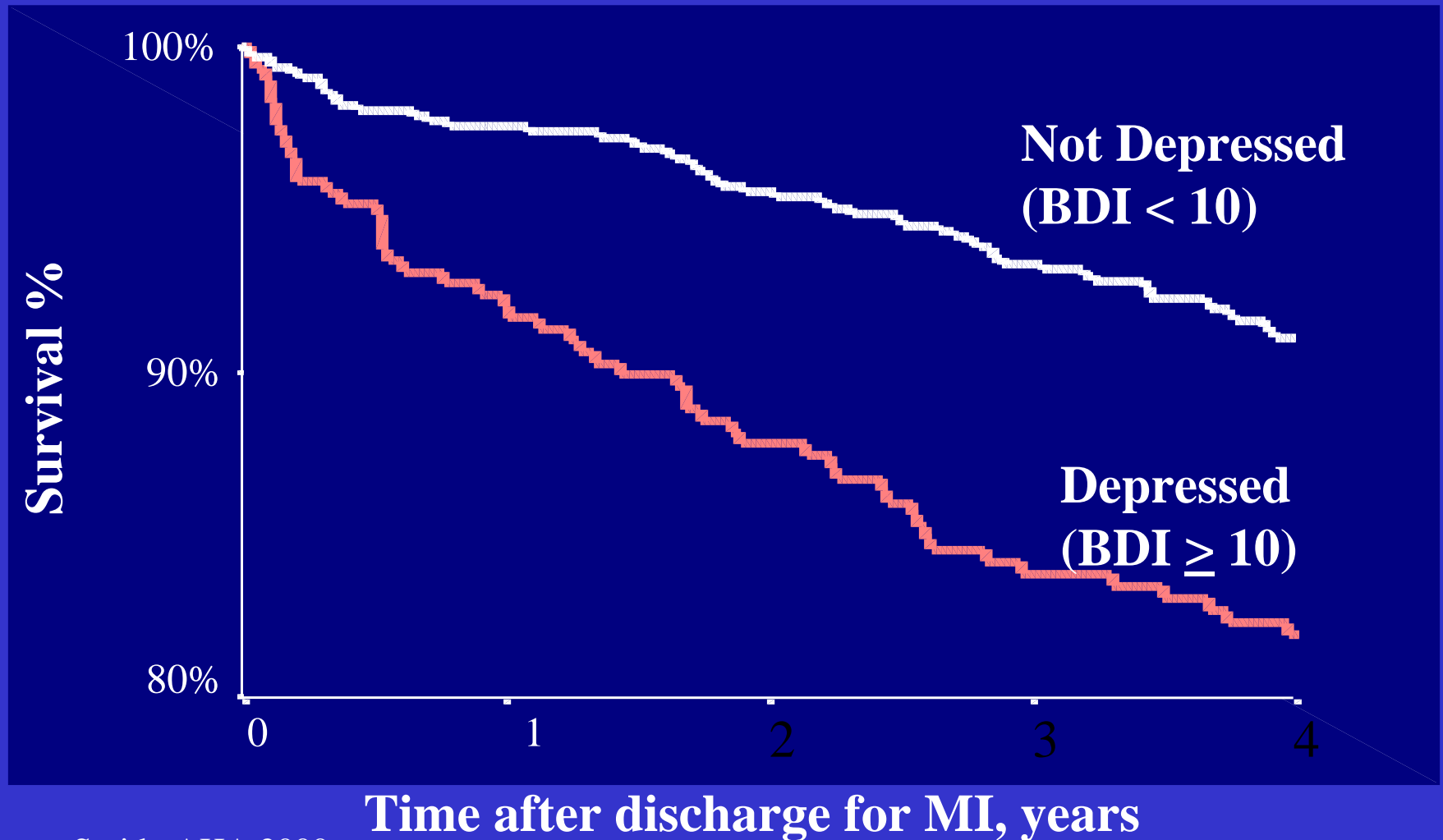
Social Support and Post-MI Cardiac Mortality.



Background

- Depression before or after MI is associated with an increased risk of death and recurrent infarction
- Adjusted risks range from 2.2 – 4.4
 - Bush, *AJC*, 2001; Irvine, *Psych Med*, 1999; Frasure-Smith, *JAMA*, 1993; Ahern, *AJC* 1990; Carney, *Psych Med*, 1988.

Depression and Post-MI Cardiac Mortality



Hypothesis

That treating of depression and low social support early after an acute myocardial infarction will reduce recurrent infarctions and death.

Inclusion Criteria

- Recruitment within 28 days after MI
- Review of medical records to verify MI
 - Characteristic increases in enzymes indicating MI (2 x ULN), and:
 - Symptoms compatible with acute MI, or
 - Characteristic evolution electrocardiographic S-T changes or new Q waves
- Diagnosis of
 - major or minor depression by DIS/HamD or
 - low social support by ESSi

Exclusion Criteria

- MI due to cardiac procedures (CABG or PTCA)
- Non-cardiac illness likely to be fatal within 1 year
- Medical condition limiting participation
- Major psychiatric comorbidity (e.g., schizophrenia, dementia)
- Imminent suicide risk
- Unwilling to provide informed consent
- Unable to complete screening visits
- Inaccessible for treatment and follow-up

Control Group

Control group: Usual cardiac and rehabilitation care; physicians notified of psychosocial test scores.

All patients: Written instructions concerning CHD risk factor modification via “An Active Partnership for the Health of Your Heart” (AHA, 1990).

Treatment Group

- Behavioral Treatment (CBT) for Depression and Low Social Support
 - Individual Sessions
 - Group Sessions
 - SSRI for non-responders and severely depressed (HamD > 24)

Assuring Intervention Integrity

Centralized training for delivery of CBT.

Treatment manual, with specific CBT goals.

Audiotaping of all therapy sessions, with expert review of randomly selected tapes.

Regularly scheduled conference calls among therapists.

Site visits and therapy goals review by expert staff.

Primary Endpoint

- All-cause mortality plus non-fatal myocardial infarction
- Assumptions:
 - usual care event rate = 23% over 3.5 years
 - 25% non-compliance
 - alpha = .05, adjusted for multiple looks
- 88% power to detect 30% reduction in events for complying patients, N = 3,000

Secondary Endpoints

- All-cause mortality
- Cause-specific mortality
- Recurrent nonfatal MI
- Revascularization procedures
- Cardiovascular hospitalization

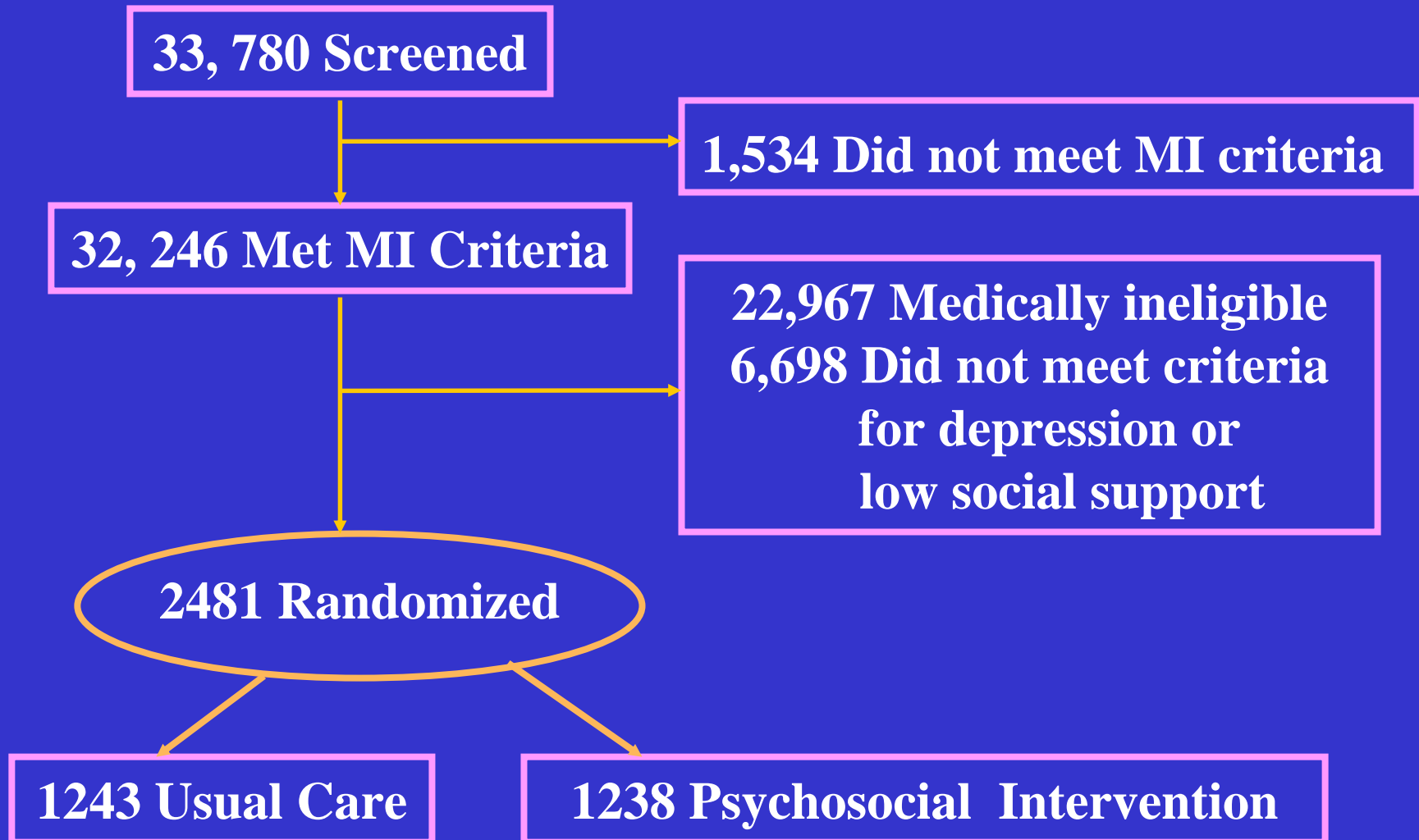
Assuring Objective Endpoints

- Endpoints reviewed by two members of a committee masked to treatment assignment
- Differences of opinion adjudicated by committee discussion
- Psychosocial outcomes evaluated by staff masked to treatment assignment

Study Design Summary

- Randomized, parallel-group clinical trial
- Post-MI patients randomly assigned to special intervention or usual care
- Average follow-up for 2.4 years
- Masked ascertainment of primary endpoint
- Intention-to-treat analysis

Screening and Enrollment



Control of Randomization

- Centralized, automated, telephone based system
- Entry of specifically required data
- Available at all times

Assuring Proper and Adequate Recruitment

- Weekly reports to PIs, with demographic subgroup information.
- Conference calls to problem sites.
- Recruitment coordinators' conference calls
- Site visits to review cardiology support, enlisting additional sources, evaluate enrollment integrity
- Re-allocation of resources

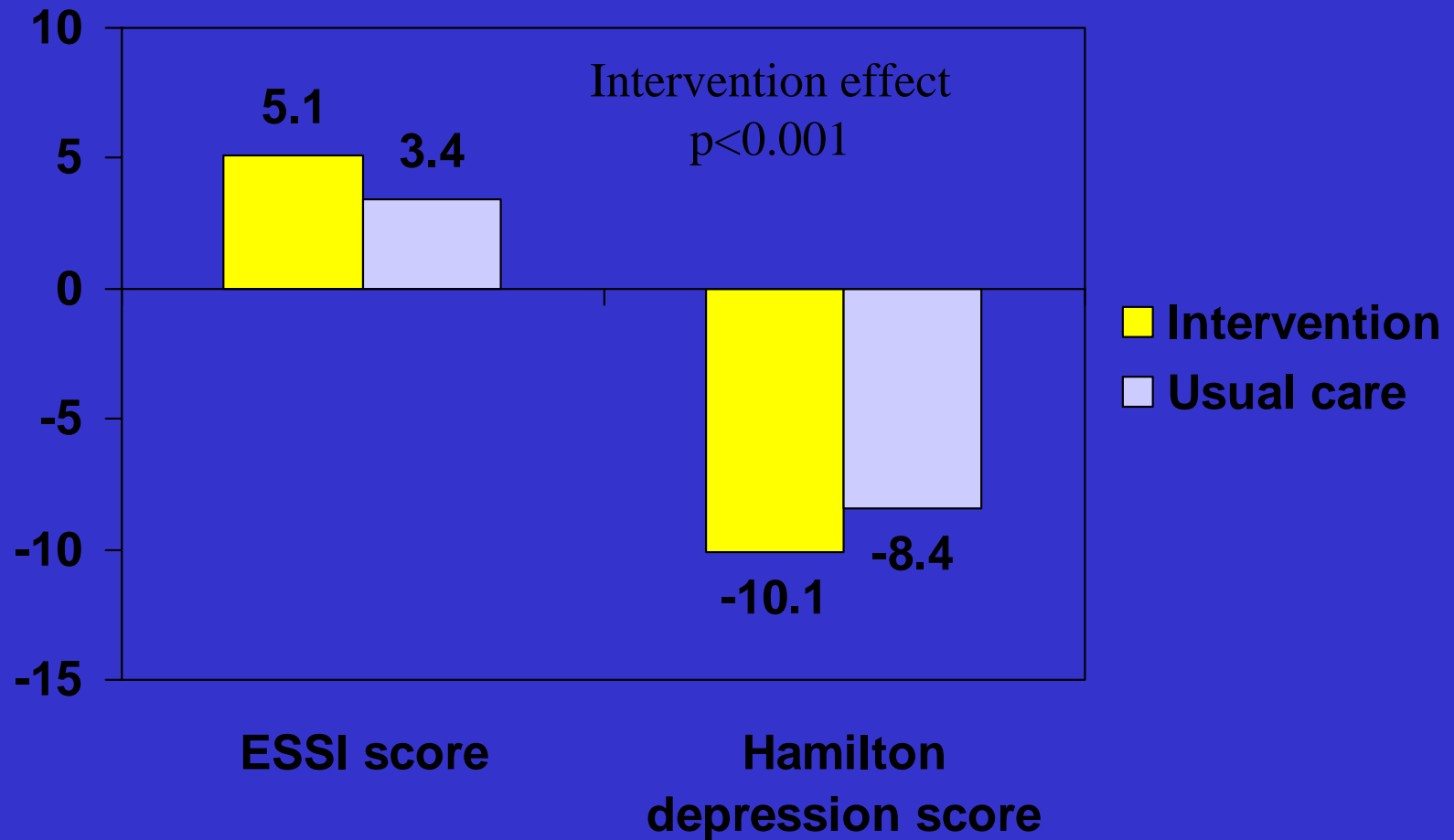
Assuring Data Completeness and Quality

- Centralized training for data collection process, forms, laboratory procedures
- Monthly reports to PIs
- Conference calls
- Site visits, with random chart review, including source documents
- Site visits for participant retention
- Site visits of Coordinating Center

Overall Monitoring

- Data and Safety Monitoring Board
 - Approval of protocol and any revisions
 - Bi-annual meetings, conference calls as needed
 - Review of recruitment, outcome data, all aspects of performance, side effects, special issues
 - Recommend continuing/stopping trial

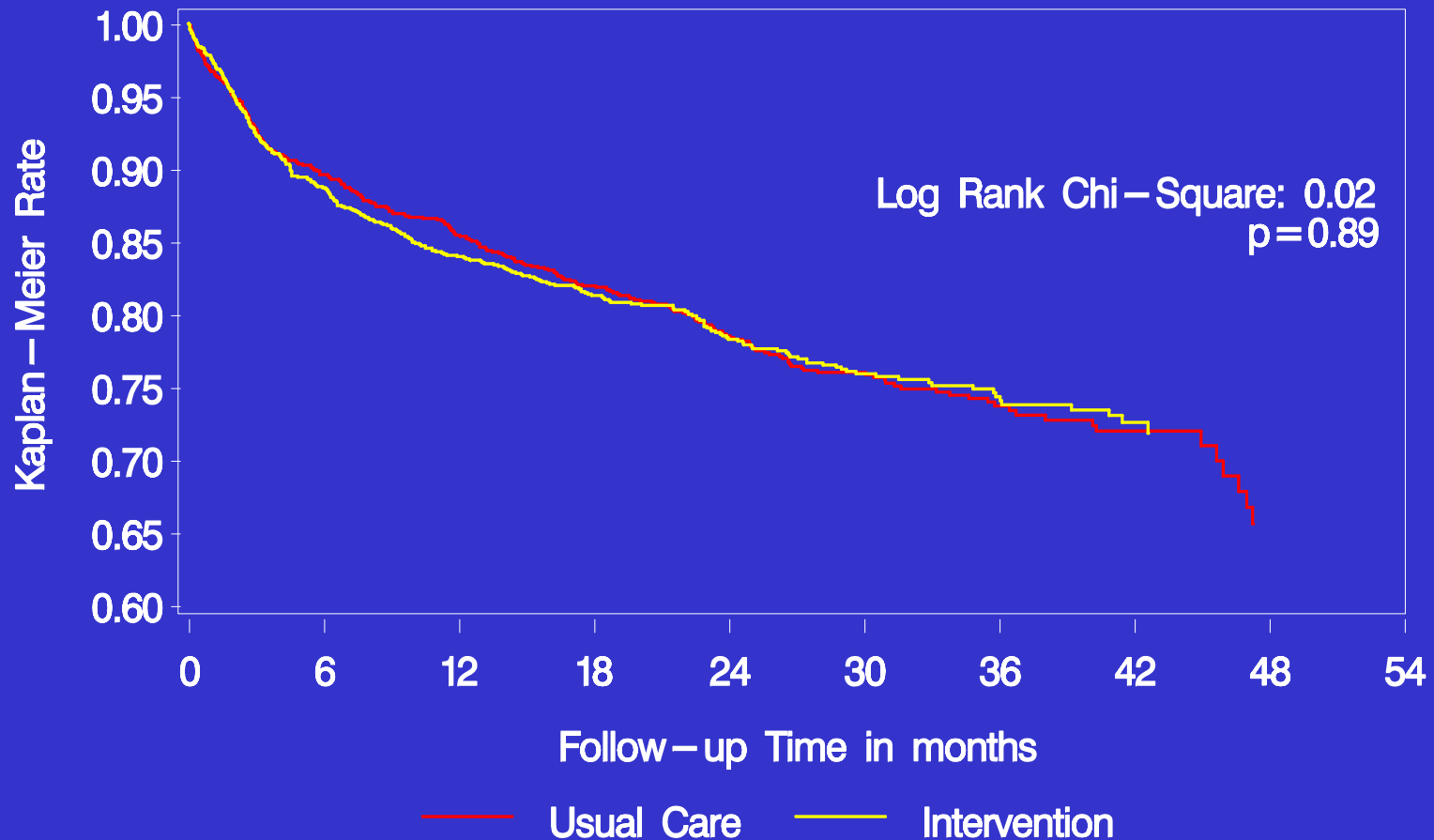
Changes in Social Support and Depression after 6 months



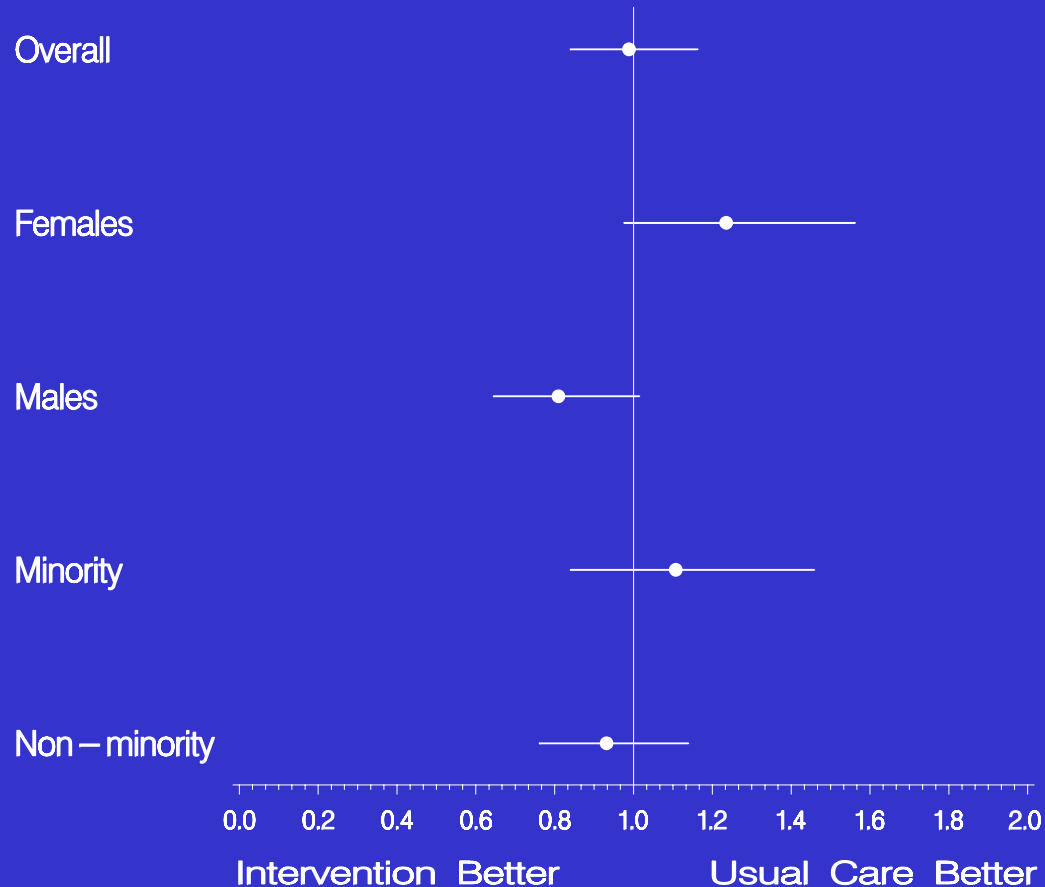
ESSI reported for patients with low social support only

Hamilton depression score reported for depressed patients only

Kaplan-Meier Survival Curves



Hazard Ratios for Pre-specified Subgroups



Conclusions

- Treating depression and low social support immediately after myocardial infarction:
 - Improves symptoms of depression and improves social support.
 - Does not reduce the higher death rate and recurrence of infarction in these patients.

Comments

- Hypothesis: was timing of intervention appropriate?
- Remission of symptoms in usual care:
Role of informing physicians of results psychosocial screening results?

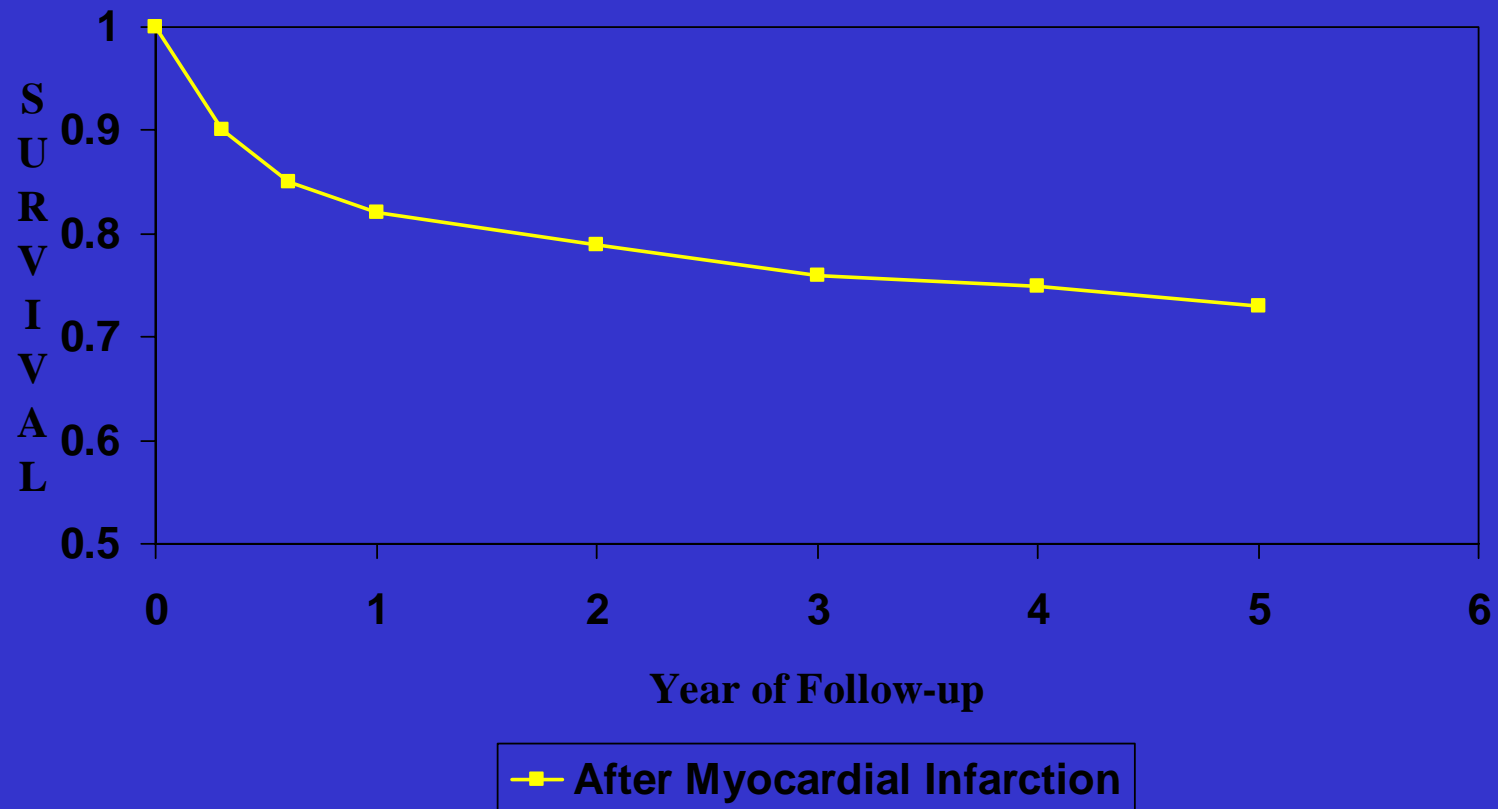
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- External vs. Self-referral by patients?
- Demographic subgroup results?
- Back to basic research?
- Do results inform clinical care?

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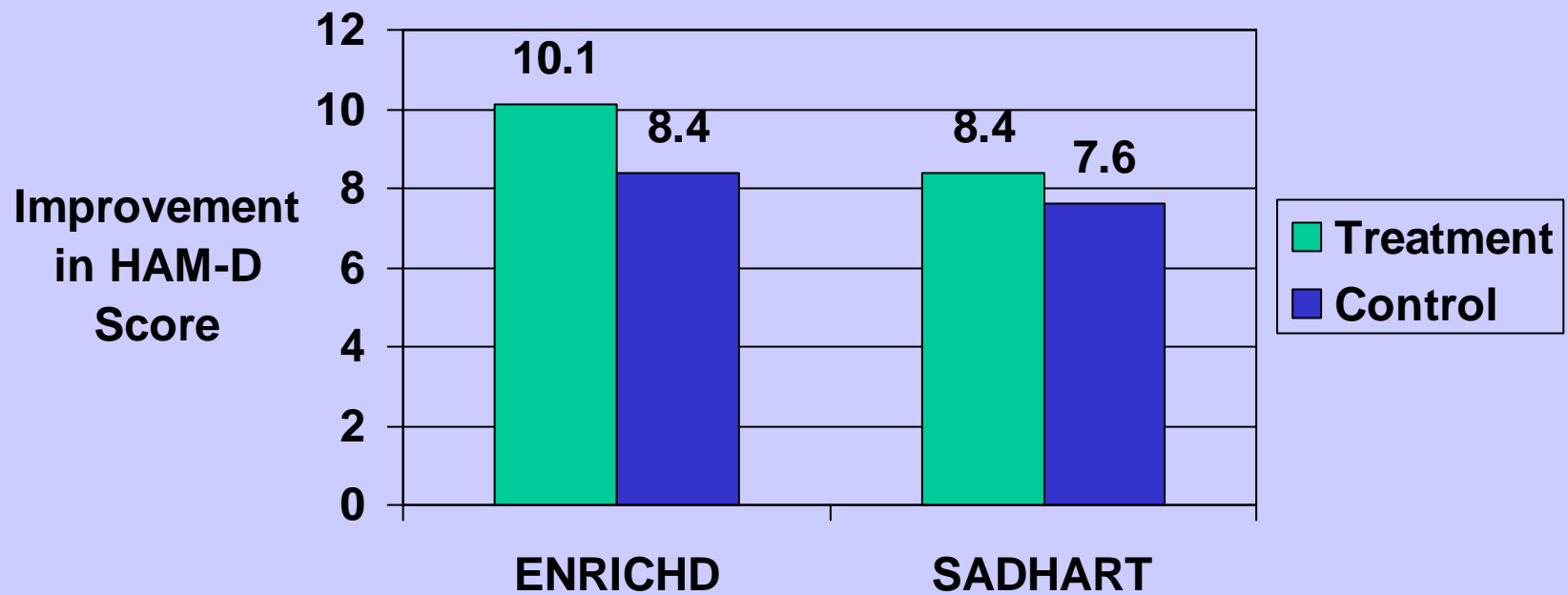
Pattern of post-MI risk



Comments

- Hypothesis: was timing of intervention appropriate?
- Remission of symptoms in usual care:
Role of informing physicians of results psychosocial screening results? ---

Change in HAM-D after treatment



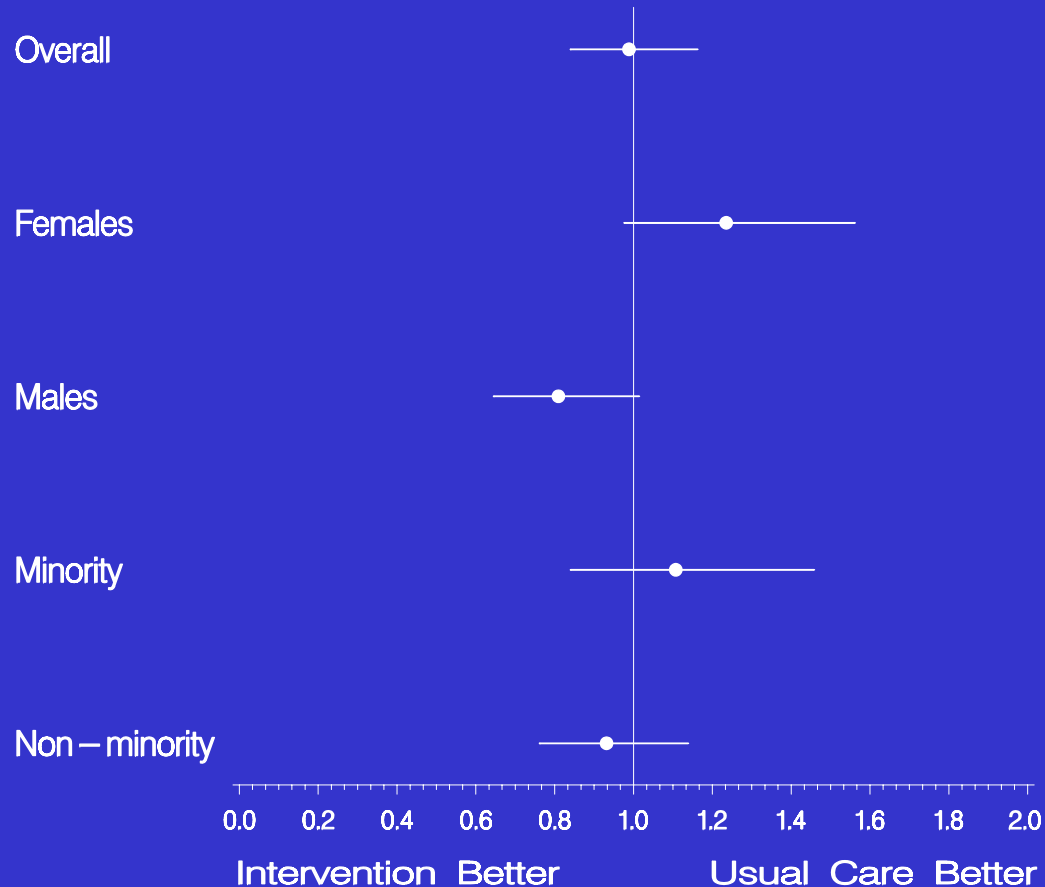
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Hazard Ratios for Pre-specified Subgroups



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Recommendation

- Depression in patients after myocardial infarction should be treated under existing guidelines for treating depression in the general population.

Important Challenges for Behavioral Research

- Identifying promising diagnostic and intervention strategies;
- Testing evidence-based interventions for each of the identified psychosocial risk factors;
- Augmenting the infrastructure for clinical research.

Psychosocial Cardiovascular Disease Risk Factors in Search of Proven Interventions

- Depression
- Low levels of social support
- Hostility
- Stress
- Health disparities?

Return to the bench?

Should we postpone clinical trials until the mechanisms through which psychosocial risk factors act are understood?

Major Avenues for Psychosocial Influences on CVD: 1971

- Elevation of other commonly reported risk factors.
- Pathological effect mediated by unspecified neuropsychological mechanisms.
- Effect on coronary patients' acceptance of medical care.

NHLBI Task Force on Atherosclerosis, 1971

Major Avenues for Psychosocial Influences on CVD: 2003

- Increased platelet activation
- Decreased resistance to inflammation and infection
- Increased sympathoadrenal tone
- Diminished adherence to healthy lifestyle
- Diminished adherence to medical regimens

The Case of Ventricular Arrhythmias and Sudden Death

- Ventricular Premature Complexes (VPCs) predispose to v. arrhythmias, sudden death.
- Long-acting, Class 1 antiarrhythmic drugs protect against VPCs;
- 3,000-patient post-marketing database.

Cardiac Arrhythmia Suppression Trial (CAST) - 1989

- n = 2309
- Post-myocardial infarction, 6 PVCs/hr
- Class 1 Antiarrhythmics: Encainide, Flecainide, Moricizine
- 10 months follow-up
- Outcome: RR of death 3.6 in favor of placebo for deaths and non-fatal events

“A remedy which is known to work,
though nobody knows why, is
preferable to a remedy which has
the support of theory without
confirmation in practice.”

Richard Asher
Lancet, 1961

Factors involved in “decisions about care”

- Diagnosis
- Prognostic markers
- Clinically relevant research
- Clinical experience
- Patient's preferences

Evidence-Based Medicine

“the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients...”

David L. Sackett

BMJ, 1996

Discussion and Debate

- Society of Behavioral Medicine and APA Division 38, Health Psychology: Evidence-based behavioral medicine committee: www.sbm.org
- AAPB / SNR Task Force on Methodology and Empirically Supported Treatments: Template for evaluating clinical efficacy of interventions.
- Office of Behavioral and Social Sciences Research, NIH: Two-week seminar on Randomized Clinical trials Involving Behavioral Interventions.